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Hemodynamic Effects of Epinephrine in Healthy and Hemorrhagic Shock Rats

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ABSTRACT

OBJECTIVE: The aim of this study was to investigate the hemodynamic effects of epinephrine intravenous injection in healthy and hemorrhagic shock rats.

METHODS: Forty Sprague-Dawley male rats weighing 250 to 300 g were randomly assigned to 4 groups: group NE, healthy rats receiving epinephrine 2 μg/kg; group NS, healthy rats receiving normal saline; group SE, hemorrhagic shock rats receiving epinephrine 2 μg/kg; and group SS, hemorrhagic shock rats receiving normal saline. Mean arterial blood pressure (MAP) and heart rate (HR) were recorded at the following time points: 0 seconds (baseline), 5 seconds, 15 seconds, 30 seconds, 1 minute, 2 minutes, 4 minutes, 6 minutes, 8 minutes, and 10 minutes (T_{0-9}) after intravenous injection.

RESULTS: There were no significant differences in MAP and HR at baseline between groups NS and NE or between groups SS and SE. Compared with the figures for baseline, MAP had no significant change at all time points in groups NS and SS. MAP increased at T_{1-9} in group SE ($P < 0.01$). MAP increased at T_{1-3} and decreased at T_{5-6} in group NE ($P < 0.01$). There was no significant change in HR in all groups after epinephrine or normal saline injection.

CONCLUSION: Epinephrine 2 μg/kg intravenous injection elicited biphasic changes in blood pressure, which included an initial increase and a subsequent decrease in healthy rats and induced a remarkable increase in blood pressure in hemorrhagic shock rats. (*Curr Ther Res Clin Exp.* 2011;72:243–249)

KEY WORDS: epinephrine, health, hemodynamics, hemorrhagic shock, rats.

INTRODUCTION

Epinephrine activates α- and β-adrenoceptors. The effects include positive inotropic, chronotropic, and enhanced conduction in the heart (β_1); relaxation of smooth muscle in the vasculature and bronchial tree (β_2); and vasoconstriction (α_1). The hemodynamic effects of epinephrine are dose dependent.[1] A rate of 1 to 2 μg/min should predominantly

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activate β_2-receptors; a rate of 2 to 10 μg/min should predominantly motivate β_1-receptors; and a rate of >10 μg/min should cause marked α-stimulation.[1]

Epinephrine used in local anesthetics has the advantages of prolonging the duration of anesthesia, increasing the intensity of nerve block, decreasing the systemic toxicity of anesthetics, and reducing the blood loss of incision. However, the systemic effects of epinephrine are variable.[1] Recent studies have shown that local infiltration of epinephrine may induce transient hypotension episodes during endoscopic sinus surgery and neurosurgery, possibly because of the activation of β_2-receptors with general anesthesia.[2–4] Our previous study demonstrated a biphasic change in blood pressure, including initial hypertension and subsequent hypotension after an intravenous bolus of epinephrine in healthy rats.[5] Linton and Linton have also observed that a small bolus dose of epinephrine can produce an initial increase in mean arterial blood pressure (MAP) followed by a much greater reduction thereafter, which may cause hypotension before cardiopulmonary bypass in patients undergoing cardiac surgery.[6]

Epinephrine is used intravenously in life-threatening circumstances, including the treatment of cardiac asystole, circulatory collapse, and anaphylaxis.[1] In shock states, epinephrine is often administrated intravenously to increase blood pressure. However, some studies have shown that intravenous injection of epinephrine may elicit a remarkable decrease in blood pressure after an initial increase, which is detrimental to patients, especially in shock states.[5,6] As of now, there is no report regarding whether an intravenous bolus of epinephrine can induce biphasic changes of blood pressure when treating shock states. Therefore, we designed a prospective, randomized, single-blinded, controlled study to observe the hemodynamic changes after an intravenous bolus of 2 μg/kg epinephrine in healthy and hemorrhagic shock rats.

MATERIALS AND METHODS

Animals

The present study was performed from September 2010 to September 2011 in Research Labs, Department of Anesthesiology, Jinling Hospital, Nanjing, China. The experimental protocol of this study was reviewed and approved by the Animal Investigation Ethics Committee of Jinling Hospital. Forty healthy Sprague-Dawley male rats, weighing 250 to 300 g, were randomly allocated into 4 groups by a random digits table with 10 rats in each group: group NE, epinephrine 2 μg/kg for healthy rats; group NS, normal saline 0.3 mL for healthy rats; group SE, epinephrine 2 μg/kg for hemorrhagic shock rats; and group SS, normal saline 0.3 mL for hemorrhagic shock rats.

Study Protocol

All rats were anesthetized with an intraperitoneal administration of 45 mg/kg sodium pentobarbital. The right femoral veins were cannulated to receive the injection of epinephrine or normal saline, and the left femoral arteries were cannulated to measure MAP in all rats. The right femoral arteries were cannulated for bloodletting to establish the model of hemorrhagic shock rats in groups SE and SS. The cannulations of each rat were completed within 35 to 40 minutes. Then, a 20-mg/kg

supplemented dose of sodium pentobarbital was intraperitoneally injected to maintain a certain depth of anesthesia. Ten minutes later, when the rats achieved a relatively steady depth of anesthesia, approximately 35% of the total blood volume was withdrawn from the right femoral arteries into a syringe containing 2 mL of normal saline and 20 units of heparin within 20 minutes, and MAP declined to 50% of the initial MAP before experimental intervention (which was defined as shock in the present study) in groups SE and SS.[7] MAP of shock level was maintained for 30 minutes with further blood withdrawal or reinfusion as required. After that, normal saline 0.3 mL or epinephrine 2 μg/kg diluted to 0.3 mL with normal saline was injected intravenously within 3 seconds.[5] In groups NS and NE, normal saline 0.3 mL or epinephrine diluted to 0.3 mL with normal saline was injected approximately 1 hour after the supplemented dose of pentobarbital. After saline or epinephrine injection, lactated Ringer solution was infused intravenously at the rate of 10 mL/kg/h in all the groups. Throughout the procedure, an appointed investigator injected epinephrine or normal saline, and another investigator who was blinded to the grouping recorded the relevant data via video snapshot.

Hemodynamic Monitoring

MAP and heart rate (HR) were recorded at the following time points: 0 seconds (baseline), 5 seconds, 15 seconds, 30 seconds, 1 minute, 2 minutes, 4 minutes, 6 minutes, 8 minutes, and 10 minutes (T_{0-9}) after intravenous injection. The highest and the lowest MAPs during this period in groups NE and SE were also observed.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc., Version 13.0, Chicago, Illinois). Quantitative data are expressed as mean (SD) and ordinal data as percentage or proportion. After a test for homogeneity of related variances, baseline hemodynamics were analyzed by independent sample *t* tests. Intragroup comparisons of MAP and HR were tested by ANOVA for repeated measurements, followed by the least significant difference tests for pair comparisons. Intergroup comparisons of MAP and HR between 2 groups of healthy rats and 2 groups of shock rats were tested by ANCOVA (dependent variable: MAP or HR; fixed factor: group; covariate: baseline MAP or HR). A P value of < 0.05 was considered statistically significant.

RESULTS

MAP and HR had no significant difference at baseline (T_0) between groups NS and NE or between groups SS and SE. Compared with the figures for baseline, MAP had no significant change at all time points in groups NS and SS. MAP increased at T_{1-9} in group SE ($P < 0.01$), but in group NE, MAP increased at T_{1-3} and decreased at T_{5-6} ($P < 0.01$). In groups NE and SE, MAP was highest at about 18 seconds and lowest at 2.1 (0.3) minutes and 1.3 (0.7) minutes, respectively. Compared with group NS, MAP increased at T_{1-3} and decreased at T_{5-6} in group NE ($P < 0.01$). Compared with group SS, MAP increased at T_{1-9} in group SE ($P < 0.01$) (Table I).

Table I. Mean arterial pressure at different time points (n = 10, mm Hg, mean [SD]).

Group	0 sec	5 sec	15 sec	30 sec	1 min	2 min	4 min	6 min	8 min	10 min
NS	122 (17)	119 (17)	119 (17)	120 (17)	120 (16)	120 (17)	121 (18)	122 (17)	120 (14)	120 (16)
NE	120 (18)	149 (21)[†,§]	168 (19)[†,§]	136 (23)[*,‡]	119 (17)	80 (7)[†,§]	91 (8)[†,§]	105 (15)	108 (15)	113 (18)
SS	45 (4)	47 (3)	49 (3)	50 (5)	50 (7)	50 (8)	49 (8)	47 (7)	48 (7)	49 (6)
SE	46 (4)	90 (6)[†,§]	122 (13)[†,§]	103 (13)[†,§]	70 (12)[†,§]	74 (14)[†,§]	74 (20)[†,§]	73 (20)[†,§]	70 (19)[†,§]	70 (18)[†,§]

[*] $P < 0.05$. Compared with baseline within each group using ANOVA for repeated measurements.

[†] $P < 0.01$.

[‡] $P < 0.05$. Compared group NS with group NE or compared group SS with group SE.

[§] $P < 0.01$.

Table II. Heart rate at different time points (n = 10, beats/min, mean [SD]).

Group	0 sec	5 sec	15 sec	30 sec	1 min	2 min	4 min	6 min	8 min	10 min
NS	376 (21)	364 (27)	363 (25)	372 (30)	362 (20)	365 (26)	361 (24)	368 (26)	373 (27)	369 (21)
NE	374 (18)	343 (38)	349 (60)	361 (51)	368 (47)	370 (30)	366 (27)	361 (29)	356 (26)	358 (24)
SS	387 (58)	384 (49)	391 (43)	377 (42)	377 (45)	375 (46)	392 (45)	387 (46)	380 (53)	377 (52)
SE	404 (36)	388 (25)	378 (67)	390 (46)	377 (49)	36 (51)	374 (42)	369 (45)	368 (45)	365 (48)

Heart rate had no significant change at different time points in all groups after epinephrine or normal saline injection.

There was no significant change in HR at different time points in all groups after epinephrine or normal saline injection ($P > 0.05$) (**Table II**).

DISCUSSION

The present study applied an animal model to evaluate the hemodynamic effects of a bolus of epinephrine in healthy and hemorrhagic shock rats. This study showed that epinephrine 2 μg/kg could produce biphasic changes in MAP in healthy rats; by contrast, in hemorrhagic shock rats, a remarkable increase in MAP occurred after epinephrine 2 μg/kg intravenous injection instead of the biphasic change.

The changes in MAP in this study may be attibuted to plasma concentrations of epinephrine with α- and β_1-effects predominating at high doses and with β_2-effects predominating at low doses.[6] After investigating the rapid changes in cardiac output and systemic vascular resistance produced by intravenous epinephrine (5 μg) with a beat-by-beat monitoring, Linton and Linton observed that epinephrine produced an initial increase in systemic vascular resistance and MAP, which was followed by a much greater reduction in patients without cardiopulmonary bypass. In addition, although cardiac output increased during the period of vasodilation, the increase was insufficient to prevent a reduction in MAP.[5]

On the other hand, MAP increased after epinephrine intravenous injection only in hemorrhagic shock rats. The mechanism might be explained by the enhanced myocardial contractility and the increased stroke volume with the effects of β_1-receptors, which surpassed the vasodilatation effects of β_2-receptors. Moreover, it might be correlated with the release of catecholamine with the effects of sympathetico-adrenomedullary system in shock states and the release of vasoexcitor materials, such as angiotensin, antidiuretic hormone, thromboxane A_2, endothelin, and so on.[8] Mink and coworkers demonstrated that in ragweed shock protocol, an intravenous bolus of epinephrine, 0.01 to approximately 0.025 mg/kg, caused only an initial increase in MAP, which was accompanied by a simultaneous increase in cardiac output, and showed that a bolus of epinephrine did not hasten the time to recovery of systemic hemodynamics in anaphylactic shock.[9,10]

Usually, when MAP increased, HR decreased, most likely due to the effect of the baroreceptor reflex being stronger than that of the activation of β_1-receptors after epinephrine used.[1] Conversely, HR increased when MAP decreased. Although there

were no significant changes of HR observed in this study, the possible major reason for this lack of change may be arributed to the balanced effects of baroreceptor reflex and the activation of β_1-receptors.

LIMITATIONS OF THE STUDY

There were some limitations in the design of the present study. First, the effects on blood pressure may be related to the blood levels of epinephrine. Thus, it would be interesting to measure the plasma concentrations of epinephrine after an intravenous bolus when significant changes of MAP appeared. Second, we should insert a pulmonary artery catheter to monitor cardiac output, stroke volume, central venous pressure, and systemic vascular resistance to better interpret the results of the present study.

CONCLUSION

From the results of the present study, we conclude that an intravenous bolus of epinephrine may cause different hemodynamic changes in healthy and hemorrhagic shock rats. In healthy rats, an intravenous bolus of epinephrine 2 μg/kg produces an initial hypertension and a subsequent hypotension. In hemorrhagic shock rats, however, an intravenous bolus of epinephrine 2 μg/kg leads only to an increase in blood pressure.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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